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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/670,119	06/25/96	NG	G SIM-001 (7434

18M1/1023

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1817	9

DATE MAILED: 10/23/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 7/2/97.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~or thirty days~~, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 18-37 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 18-37 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims 18-37 were ~~are subject~~ to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

DETAILED ACTION

Election/Restriction

1. Applicant's election of Group II in Paper No. 8 is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). It is also noted that claims 1-17 and 38-59 are now cancelled.

Claim Objections

2. Claim 37 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claim 37 has not been further treated on the merits.

Claim Rejections - 35 USC § 112

3. Claims 18-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification proposes specifically inhibiting transmembrane receptor function of D2 and D1 receptors, β1 and β2 and α1A adrenergic receptors, EGF-tyrosine kinase receptors, dopamine transporter proteins, GABA-specific ion channel receptors, a T-cell antigen receptor, as

well as vasopressin, serotonin and angiotensin receptors, in mammalian disorders through administering transmembrane hydrophobic peptides that specifically interact with the transmembrane regions of these receptors. *In vivo a*ssays for evaluating dysfunction of D2 dopamine receptors and specific β1 and α1A adrenergic receptor activity are also disclosed on pages 38-43 of the specification. Additionally, the specification discloses that "transmembrane domains of integral membrane proteins are highly conserved in mammals" (pg. 8), that these domains "are believed to have a helical conformation and generally comprise a sequence of about 22 to 26 amino acids" (pg. 7), and that the instant invention can be used to select " an antagonist peptide *specific* for that [integral membrane] protein" (pg. 9). However, it is unknown, nor disclosed, what the metes and bounds of the recitation "preventing or treating a disorder in a mammal" entails; nor how one would know when, or if, they have successfully practiced the invention "in a mammal", as broadly claimed, using any peptide, or any biologically functionally equivalent fragment or analogue of such, that "comprises at least one transmembrane domain", etc. (i.e., as it relates to claims 18-23 & 36).

Furthermore, no written description is provided within the instant specification on what "intracellular" membrane receptors are envisioned to be specifically affected, for example, in the endoplasmic reticulum or in lysosomes (e.g., on pg. 7; as it relates to claim 20), or in prokaryotes (i.e., as it relates to claims 19-20); or what specific peptides could work in either claimed embodiment. Nor is any written description provided, for example on pages 26-28, that distinguishes the metes and bounds of (c) an ion channel, versus (d) an ion channel receptor, such

as the GABA-A receptor, versus (e) a channel protein (i.e., as it relates to claim 22). Nor is any written description provided on pages 20 and 22 that describes what "substance abuses" are envisioned to be treatable (i.e., as it relates to claim 28).

Thirdly, a method of treating or preventing any disorder that involves altered integral membrane protein expression requires administration of specific peptides within sufficient proximity of the affected cell population to have any putative effect. In contrast, the specification provides no guidance, nor written description, on how to determine when a patient is in need of such treatment; nor what symptoms are envisioned to be treated; nor how the severity of these symptoms is related to the efficacy of an integral membrane receptor expression; nor how one would know when such administration is appropriate (e.g., especially as it relates to the disorders of claim 28 that have no known origin or cause). The skilled artisan also can not successfully predict when, or if, the instant invention works *in vivo*, because the parameters that need to be addressed for assaying whether the instant invention is effective in "preventing or treating a disorder in a mammal" are not disclosed, or not known, except for decreasing heart rate using a β1-adrenergic-specific peptide (pg. 41). For example, although an assay is described that induces asymmetric body posture in rats by acting as a D2 antagonist following intracerebral injection into the striatum, a disease state such as Parkinson's disease is characterized by dopamine receptor inactivity, versus overactivity. Further, in that vehicle gave a comparable change in blood pressure as the β1-adrenergic-specific peptide (pg. 42), treatment of hypertension does not appear to work using these transmembrane peptide molecules (i.e., as it relates to claims 33 and 35).

Accordingly, no functional assays are disclosed for the full scope of that claimed for determining when treatment is effective, or when needed; especially for any "disorder... characterized by disordered function of an integral membrane protein...".

The claims are further not commensurate in scope with the guidance and written description provided in the specification, in that the mechanism resulting in a disorder by one causative factor is not predictive of the mechanism/treatment of a disorder by a different causative factor, which may not involve altered integral membrane receptor expression. For example, disorders of the nervous system include neuronal cell damage that often results in cell death (i.e., as it relates to claim 28). Therefore, "administration" of any "peptide" molecule to treat neurons within the CNS requires solutions to selectively target responsive cells within the area of injury, and across the blood brain barrier, with a sufficient dosage of the specific peptide prior to neuronal cell death. However, neurons do not regenerate in the CNS (i.e., neurons die and thus can not be effectively treated; see Jackowski, pg. 305, last *pp*). Accordingly, there is no nexus for any expectation that merely administrating transmembrane-specific peptides for affecting one symptom of one disorder can be extrapolated to "treating or preventing" the full scope of symptoms encompassed by the claims (e.g., as it relates to pages 1493, 1494, 1619-1620, 1550 or 2657 of the Merck Manual). Thus, effective treatment of schizophrenia, Huntington's disease, Tourette's syndrome and any general substance abuse would not be expected to be successfully treated or prevented without undue experimentation to determine such (i.e., as it relates to claim

28), because no written description or assays are described in the specification to determine when, or if, the instant invention works *in vivo* to treat any of these particular disease states.

Lastly, the name "effective fragment or analogue thereof" (as it relates to how it is defined on pages 7-9 of the specification), does not sufficiently characterize and enable the peptides that are encompassed by the claims, because the inclusion of any "biologically functional equivalent" within the definition of "fragments or analogues" of a integral transmembrane peptide sets forth no structural characterization and little functional characteristics (i.e., as it relates to claims 18, 25-26, 30 & 33). Moreover, the specification does not teach which particular amino acids are critical for any integral transmembrane peptide's function, nor what structural features distinguishes the claimed peptides from any other peptide without the desired function of the instant invention. The specification also does not provide any evidence that any "fragment or analogue" of any transmembrane peptide possesses the desired biological activity of a receptor antagonist, except for possibly the two peptide fragments depicted in SEQ ID NOs. 30 and 31. Therefore, because the terms "fragment or analogue thereof" encompass deletions, insertions, truncations and substitutions (conservative or non-conservative) of different peptide molecules, and because the specification does not disclose those amino acid residues that are critical for inhibiting function of integral membrane receptors, nor which residues can be altered and still maintain the desired functional activity of the instant invention, the resultant random mutations and truncations to peptides with limited characterization would be predicted by the skilled artisan to result in inactive peptides. For example, Rudinger states on page 3 that "it is impossible to

attach a unique significance to any residue in a sequence. A given amino acid will not by any means have the same significance in different peptide sequences, or even in different positions of the same sequence". Rudinger further states on page 6 that "the significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study". Thus, the lack of guidance provided in the specification, as to what minimal structural requirements are necessary for inhibiting function of integral membrane activity, or assays to determine such, would prevent the skilled artisan from determining whether any random peptide "fragment or analogue" could be made that retains the desired function of the instant invention, because the 3-dimensional conformation (i.e. the helical conformation) of a native transmembrane protein would be predicted to be adversely altered by such random mutations/truncations without undue experimentation to determine otherwise.

4. Claims 19-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is ambiguous how interruption of a "prokaryotic" membrane protein can be used to treat or prevent a "mammalian" disorder.

Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite because in is unclear how an "intracellular" membrane exists in a prokaryote.

Claim 18 & 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite because it is ambiguous how a peptide "fragment or analogue thereof" can comprise "at least one" or a "plurality of transmembrane domains".

Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite because the distinction between (c) an ion channel, (d) an ion channel receptor, and (e) a channel protein is not clear.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 18-22 & 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Lofts et al. Lofts et al. teach treatment of nude mice with an effective amount of a WT peptide sequence (see pg. 2814, Fig. 1), which comprises at least one transmembrane domain of the mammalian *neu* integral plasma membrane protein (i.e., as it relates to a plurality of transmembrane domains in a ~~tyrosine kinase receptor which extends intracellularly~~; as recited in claims 20-22 & 36), such that growth of solid tumors in these mice was reduced (pgs. 2816-2817).

6. Claims 18-24, 29 & 36 are rejected under 35 U.S.C. 102(e) as being anticipated by Murphy et al.

Murphy et al. teach use of dopaminergic (col. 13, lines 29-49; i.e., as it relates to claims 22-24) and adrenergic (col. 16 line 60-col. 27, line 10; i.e., as it relates to claims 22-23 & 29) G-protein-coupled transmembrane receptor peptides in pharmaceutical compositions to "treat or prevent" G-protein-related diseases (cols. 35-37; as it relates to claims 18-21 & 36).

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

RCH

Robert C. Hayes, Ph.D.
October 10, 1997

PAULA K. HUTZELL
SUPERVISORY PATENT EXAMINER
GROUP 1800